(12) UK Patent Application (19) GB (11) 2 185 887 (13) A

(43) Application published 5 Aug 1987

(21) Application No 8602664

(22) Date of filing 4 Feb 1986

(51) INT CL⁴
A61K 31/55

(52) Domestic classification (Edition I)
A5B 180 230 23Y 272 27Y 280 28Y 301 30Y 351 35Y 401 402 40Y 480 48Y 502 503 50Y 552 55Y 577 57Y 586 58Y 616 61Y 650 65Y J
U1S 2417 A5B

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(56) Documents cited
GB 1345510
The Theory and Practice of Industrial Pharmacy Lachman Lieberman and Kanig 2nd edition, pages 541-566 page 563

(58) Field of search
A5B
Selected US specifications from IPC sub-class A61K

(54) Temazepam composition

(57) A liquid preparation of temazepam which is for oral administration comprises not more than 0.2% w/v temazepam, not more than 15% w/v of at least one polymeric alochol, not less than 8% w/v a low boiling alcohol, not less than 40% w/v glycerol, not more than 45% of an aqueous solution of at least one hexahydric alcohol, a solubilizer, at least one flavouring agent and at least one buffering agent for maintaining the pH of the composition at from 7.3 to 8.3.

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SPECIFICATION

Temazepam Compositi n

This invention relates to a temazepam (3-hydroxydiazepam) composition and to a process for preparing the same.

In particular, the invention relates to a liquid preparation of temazepam which is suitable for oral administration. Capsules containing temazepam for oral administration are already known and the aim of developing a liquid preparation of the drug was to promote more rapid absorption and thus fast sleep induction, as well as to provide practitioners and patients with a useful choice.

Temazepam is only slightly soluble in water and is unstable in aqueous solution. Thus, on standing, temazepam itself and its decomposition products tend to precipitate out of aqueous solution. On the other hand, non-aqueous solvents are generally unacceptable for human consumption.

It is an object of the present invention to enable the provision of a liquid preparation of temazepam which is suitable for oral administration and palatable, whilst having an acceptable shelf life and viscosity.

Accordingly, the invention provides a temazepam composition which comprises not more than about 0.2% w/v temazepam, not more than about 15% w/v of at least one polymeric alcohol, not less than about 8% w/v a low boiling alcohol, more particularly a monohydric alcohol such as methanol, ethanol or isopropanol, preferably ethanol, not less than about 40% w/v glycerol, not more than about 45% of an aqueous solution of at least one hexahydric alcohol, a solubilizer, at least one flavouring agent and at least one buffering agent for maintaining the pH of the composition at from 7.3 to 8.3, as well as a process for preparing the composition.

The concentration of temazepam is preferably about 0.2%, as this corresponds to a concentration of 10 mg/5 ml, that is to say, one normal dose per teaspoonful.

The solubilizer is provided to stabilise, disperse and complex the temazepam and flavouring agent(s) (which are generally insoluble in water) and preferably comprises polyvinylpyrrolidone (Povidone) making up at least about 2% w/v of the composition.

The composition includes a solvent system typically made up of anhydrous ethanol, glycerol, a polyethylene glycol and a hexahydric alcohol such as mannitol or sorbitol. The ethanol is required as a solvent for the temazepam, to keep the visocity of the composition at an acceptably low level during preparation and use, and as a preservative, to inhibit microbial growth. The amount of ethanol should preferably not exceed about 10%.

The polyethylene glycol may be polyethylene glycol 100 but is preferably polyethylene glycol 400. The hexahydric alcohol is preferably sorbitol, which is more readily available and has a better solubility in water than mannitol. The amount of glycerol is preferably at least about 50% w/v: this amount should not be increased too much as this would increase the osmotic pressure of the composition and lead to a "burning" taste, whilst reducing the glycerol content below about 40% will reduce its effect as a preservative.

Temazepam is pH sensitive and decomposition thereof can also alter the pH of the composition over time. Therefore, a buffering agent is required and the initial pH is preferably about 7.8. Suitable buffering agents include disodium hydrogen phosphate (sodium phosphate BP anhydrous) and citric acid monohydrate (the amount of water present in the small quantity of citric acid used being negligible).

The flavouring agent(s) may comprise peppermint oil BP and/or lemon oil. The lemon oil is preferably terpeneless, to improve its water miscibility.

The composition typically additionally comprises a colouring agent, such as chlorophyll, to improve its asesthetic appeal.

The order in which the components of the composition are mixed is important. Preferably, the process comprises combining the said aqueous solution and at least some of the buffering agent(s) to obtain a first solution A, combining at least some of the alcoholic constituents, the solubilizer and the temazapam to obtain a second solution B, combining solutions A and B, and adding the flavouring agent(s).

The invention will now be described by reference to an Example.

EXAMPLE

A composition in accordance with the invention was prepared from the constituents listed in the Table.

TABLE

	% w/v (g/100 ml)	mg/5 ml
Temazepam*	0.206	10
Povidone (Kollidon 25) BP	2.000	100
Polyethylene glycol 400 BP	5.000	250
Ethanol, absolute (anhy) BP	8.800	440
Glycerol BP	50.000	2500
Sodium phosphate (anhy) BP	2.500	125
Citric acid	0.125	6.25
Chlorophyll 'JJ'	0.012	0.60
Sorbitol solution (70%) BP	45.000	2250
Peppermint oil BP	0.035	1.75
Lemon flavour Supara SL 2300	0.060	3
Glycerol BP	To 100.000	volume/5 ml

*An average of 3% has been included. The decision to include this was based on the assay results of pilot production batches where losses of between 2 and 7% occurred. It is suggested that the losses were due to the high viscosity of the temazepam solution which is added to the glycerol.

The sorbitol syrup was dispensed into a stainless-steel vessel and heated to 60°C. The anhydrous sodium phosphate was added and mixed with a high-shear mixer until dissolved. The mixture was allowed to cool to about 40°C and the citric acid was added and mixed with a high-shear mixer until dissolved. The Chlorophyll JJ was then added and mixed with a high shear mixer until a uniformly green solution was obtained. The mixture was allowed to cool to room temperature (that is, about 20°C) over about 24 hours, to obtain Solution A.

Into a separate stainless-steel vessel was weighed the glycerol, and the polyethylene glycol 400 and 90% of the ethanol were then added and mixed with a high-shear mixer. With continued mixing, the povidone was then slowly added and mixed until dissolved. The temazepam was then added and mixed until dissolved, to obtain solution B.

The cooled solution A was added slowly to solution B, mixing with a spoon. The peppermint and lemon flavours were then added and mixed. The flavour containers were rinsed with the remaining ethanol and the washings were added to the preparation and mixed. The preparation was made up to volume with glycerol and mixed and the pH was adjusted to 7.6 to 8.0 using citric acid or concentrated sodium hydroxide solution as appropriate.

The product obtained was a clear, bright, viscous green liquid with the odour and taste of lemon and peppermint. The pH was 7.3 to 8.3 at 20°C and the weight per ml was 1.20 to 1.26 g at 20°C. Adsorption spectra showed the presence of temazepam and chlorophyll and HPLC showed the presence of 1.96 to 2.2 mg per ml (98 to 110%) of temazepam. HPLC and spectrophotofluorometric analysis showed the presence of not more than 2.5% organic impurities, including not more than 0.5% 2-methylamino-5-chlorobenzophenone and fluorescent degradation products together. GLC showed the ethanol content to be 7.4 to 9% w/v.

On standing, the specification of the product remained as set out above, except that the temazepam content decreased to not less than 1.8 mg/ml (90°) and the proportion of organic impurities increased to not more than 5%, including not more than 2.5% 2-methylamino-5-chlorobenzophenone and not more than 1.5% fluorescent degradation products. The product remained within these (acceptable) limits for not less than 2½ years.

In addition, the product was found to be acceptable in taste and to promote rapid adsorption, peak plasma levels of the temazepam being attained approximately fifteen minutes after ingestion, as compared to thirty minutes previously obtained with capsules.

CLAIMS

1. A temazepam composition which comprises not more than about 0.2% w/v temazepam, not more than about 15% w/v of at least one polymeric alcohol, not less than about 8% w/v a low boiling alcohol, not less than about 40% w/v glycerol, not more than about 45% of an aqueous solution of at least one hexahydric alcohol, a solubilizer, at least one flavouring agent and at least one buffering agent for maintaining the pH of the composition at from 7.3 to 8.3.

2. A composition according to Claim 1, which comprises about 0.2% w/v temazepam.

3. A composition according to Claim 1 or 2, wherein the solubilizer is polyvinylpyrrolidone and comprises at least about 2% w/v of the composition.

4. A composition according to any one of the preceding claims, wherein the polymeric alcohol has been obtained by polymerizing a glycol.

5. A composition according to Claim 4, wherein the polymeric alcohol is polyethylene glycol 400 or polyethylene glycol 100.

6. A composition according to any one of the preceding claims, which comprises from 5% to 15% w/v of the at least one polymeric alcohol.

7. A composition according to Claim 6, which comprises about 5% of the at least one polymeric alcohol.

8. A composition according to any one of the preceding claims, which comprises from 8 to 10% ethanol.

9. A composition according to Claim 8, which comprises 8.8% w/v ethanol.

10. A composition according to any one of the preceding claims, which comprises at least about 50% w/v glycerol.

11. A composition according to any one of the preceding claims, wherein the hexahydric alcohol is mannitol or sorbitol.

12. A composition according to Claim 11, wherein the aqueous solution is a 70% solution of sorbitol.

13. A composition according to any one of the preceding claims, wherein the initial pH of the composition is from 7.5 to 8.

14. A composition according to Claim 13, wherein the initial pH of the composition is at least about 7.6.

15. A composition according to Claim 14, wherein the initial pH of the composition is about 7.8.

16. A composition according to any one of the preceding claims, wherein the at least one buffering agent comprises sodium phosphate and/or citric acid.

17. A composition according to any one of the preceding claims, wherein the at least one flavouring agent comprises peppermint oil and/or lemon oil.

18. A composition according to Claim 17, which comprises terpeneless lemon oil.

19. A composition according to any one of the preceding claims, further comprising a colouring agent.

20. A composition according to Claim 19, wherein the colouring agent is chlorophyll.

21. A process for preparing a composition in accordance with any one of the preceding claims.

22. A process for preparing a temazepam composition, which process comprises combining not more than about 0.2% w/v temazepam, not more than about 15% w/v of at least one polymeric alcohol, not less than about 8% w/v ethanol, not less than about 40% w/v glycerol, not more than about 45% of an aqueous solution of at least one hexahydric alcohol, a solubilizer, at least one flavouring agent and at least one buffering agent for maintaining the pH of the composition of from 7.3 to 8.3.

23. A process according to Claim 22, which comprises combining the said aqueous solution and at least some of the buffering agent(s) to obtain a first solution A, combining at least some of the alcoholic constituents, the solubilizer and the temazepam to obtain a second solution B, combining solutions A and B, and adding the flavouring agent(s).

24. A process according to Claim 23, wherein the aqueous solution is heated prior to the addition of the buffering agent(s) and solution A is cooled to room temperature before combining solutions A and B.

25. A process according to Claim 24, wherein at least one colouring agent is added to solution A whilst solution A is above room temperature.

26. A process according to any one of Claims 22 to 25, further comprising adjusting the pH of the composition to 7.6 to 8.0.

27. A process according to any one of Claims 22 to 26, wherein the percentage of temazepam combined with other composition ingredients is 0.206% w/v.

28. A process according to any one of Claims 22 to 27, wherein the solubilizer is polyvinylpyrrolidone and the percentage thereof combined with other composition ingredients is at least about 2% w/v.

29. A process according to any one of Claims 22 to 28, wherein the polymeric alcohol has been obtained by polymerizing a glycol.

30. A process according to Claim 29, wherein the polymeric alcohol is polyethylene glycol 400 or polyethylene glycol 100.

31. A process according to any one of Claims 22 to 30, wherein the percentage of the at least one polymeric alcohol combined with other composition ingredients is from 5% to 15% w/v.

32. A process according to Claim 31, wherein the percentage of the at least one polymeric alcohol combined with other composition ingredients is about 5% w/v.

33. A process according to any one of Claims 22 to 32, wherein the percentage of ethanol combined with other composition ingredients is from 8 to 10% w/v.

34. A process according to Claim 33, wh rein the percentage of ethanol combined with other composition ingredients is 8.8% w/v.

35. A process according to any one of Claims 22 to 34, wherein the percentage of glycerol combined with other composition ingredients is at least about 50% w/v.

36. A process according to any one of Claims 22 to 35, wherein the hexahydric alcohol is mannitol or sorbitol.

37. A process according to any one of Claims 22 to 36, wherein the aqueous solution is a 70% solution of sorbitol.

38. A process according to any one of Claims 22 to 37, wherein the at least one buffering agent comprises sodium phosphate and/or citric acid.

39. A process according to any one of Claims 22 to 38, wherein the at least one flavouring agent comprises peppermint oil and/or lemon oil.

40. A process according to Claim 39, wherein the lemon oil comprises terpeneless lemon oil.

41. A process according to any one of Claims 22 to 40, further comprising the addition of a colouring agent.

42. A process according to Claim 41, wherein the colouring agent is chlorophyll.

43. A composition, substantially as hereinbefore described in the Example.

44. A process for preparing a composition, substantially as hereinbefore described in the Example.

45. Any novel feature or combination of features described herein.

Printed for Her Majesty's Stationery Office by Courier Press, Leamington Spa. 8/1987. Demand No. 8991685.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.